



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,435	02/15/2002	M. Vijay Kumar	M0351-268908	3474

7590 10/21/2004

Cynthia B. Rothschild
Kilpatrick Stockton LLP
1001 West Fourth Street
Winston-Salem, NC 27101

EXAMINER

DAVIS, MINH TAM B

ART UNIT PAPER NUMBER

1642

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,435	KUMAR, M. VIJAY	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 03 September 2004.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-44 is/are pending in the application.
 4a) Of the above claim(s) 1-27 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 28-44 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date 10/12/02.

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

DETAILED ACTION

Applicant's election with traverse of group 9, Claims 28-44, TRAIL polypeptide, in Paper of 09/03/04 is acknowledged and entered.

Claims 1-44 are pending in the instant application and Claims 1-27 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group 9, Claims 28-44, TRAIL polypeptide are currently under prosecution.

The traversal is on the following ground(s): search all the claims would not prove unduly burdensome.

The traverse has been considered but is found not to be persuasive for the following reasons:

Searching for the compositions of groups 7-10 together would impose serious search burden. A search of the polynucleotide of group 8, 10 would not be used to determine the patentability of polypeptide of group 9, and vice-versa. Further, the search for the composition of group 9 encompasses an extra search for the antiprogestin, which is not claimed in group 7. Moreover, the intended use for treating cancer of the composition of group 7 could not be used to determine the patentability of the composition of group 9, and vice-versa, because the composition of group 9 encompasses an extra compound not found in group 7.

Searching the methods of groups 1-6, and the composition of group 9 together would impose serious search burden. The inventions of Groups 1-6, 9 have a separate status in the art as shown by their different classifications. Prior art which teaches the

polypeptides of group 9 would not necessarily be applicable to the method of using said polypeptides. Moreover, even if the polypeptide products were known, the method of treating cancer using the products may be novel and unobvious in view of the preamble or active steps.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 28-44, TRAIL polypeptide are examined in the instant application.

OBJECTION

1. Claims 28-44 are objected to for the use of the abbreviated language "TRAIL". A full name of TRAIL is required to obviate this objection.
2. Claims 28-44 are further objected to for the use of designation "TRAIL" as the sole means of identifying the claimed polypeptide. The use of laboratory designation only to identify a particular polypeptide renders the claim indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides. Amendment of the claims to include physical and/or functional characteristics of "TRAIL" which unambiguously define "TRAIL" is required.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is indefinite for the use of the language "substantially". The term substantially in claim 32 is a relative term which renders the claim indefinite. The term substantially is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH

Claims 28-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 28-44 are drawn to a composition or a kit for treating cancer, comprising an effective amount of TRAIL and an antiprogestin sufficient to induce apoptosis in at least a portion of cancer cells exposed to said composition.

The specification discloses that TRAIL is a recent addition to the tumor necrosis factor alpha family of apoptotic inducing agents, and has sequence similarity to TNF alpha and to Fas-ligand, while citing publications known in the art (p.2, last paragraph). No further disclosure of the structure of TRAIL is found in the specification.

It is noted that TRAIL is an essential material for the claimed composition. However, MPEP 6.19 teaches that incorporation of **essential material** in the specification by reference to a foreign application or patent, or to a publication is

improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973) (see MPEP 6.19 and 6.19.01).

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

If Applicant could overcome the above 112, first paragraph, Claims 28-44 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a wild type TRAIL polypeptide and an antiprogestin for treating cancer, does not reasonably provide enablement for a composition comprising any TRAIL polypeptide, such as a variant TRAIL, or a TRAIL polynucleotide and an antiprogestin for treating cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 28-44 are drawn to :

A composition or a kit for treating cancer, comprising an effective amount of TRAIL and an antiprogestin sufficient to induce apoptosis in at least a portion of cancer cells exposed to said composition (Claims 28, 42). Said antiprogestin comprises Mifepristone (Claims 29, 30, 43). Said Mifepristone and said TRAIL are packaged such

that Mifepristone is at least partially released for application to cancer prior to the release of said TRAIL, or are released substantially simultaneously (Claim 32). The dose of TRAIL results in a local concentration of TRAIL at the tumor, which ranges from 1 to 1,000 ng/ml, 200-600 ng/ml, 350-450 ng/ml (Claims 33-35). The dose of Mifepristone results in a local concentration of TRAIL at the tumor, which ranges from 1 to 1,000 uM, or 1 to 100 uM or 5 to 20 uM (Claims 36-38). Said cancer cells comprise prostate cancer cells, or androgen responsive cells, or prostate cells that do not respond to androgen (claims 39-41, 44).

The specification discloses that TRAIL is a recent addition to the tumor necrosis factor alpha family of apoptotic inducing agents, and has sequence similarity to TNF alpha and to Fas-ligand (p.2, last paragraph).

It is noted that there is no definition of TRAIL in the specification.

In the absence of a definition of TRAIL, TRAIL encompasses wild type and variant TRAIL.

Further TRAIL encompasses TRAIL polynucleotide.

Thus Claims 28-44 encompass a composition or a kit for treating cancer, comprising an effective amount of a variant TRAIL or a TRAIL polynucleotide and an antiprogestin or Mifepristone sufficient to induce apoptosis in at least a portion of cancer cells exposed to said composition.

A. Applicants have not shown how to make and use the claimed variants which are capable of functioning or have the properties of the wild type TRAIL.

The claims read on variant TRAILs, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions. The specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. The specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated.

One cannot extrapolate the teaching in the specification to the scope of the claims because it is well known in the art that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein and that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino

acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The specification does not disclose how to make the claimed variant TRAILs, such that they would function or have the properties as claimed, or how to use said variants if they did not have the function or properties claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

B. Further, it is noted that there is no teaching in the specification what the structure is for the TRAIL polynucleotides encoding the TRAIL polypeptide.

One cannot extrapolate the teaching in the specification to the claims, because due to degeneracy of the codon, the TRAIL polynucleotides encoding the TRAIL polypeptide encompass numerous polynucleotide sequences. One cannot determine which sequence encodes the TRAIL polypeptide in view of the lack of the teaching of the coding regions of these polynucleotides, and it would be a serious burden to screen for the polynucleotide sequences encoding the TRAIL polypeptide.

Further, the claims encompasses a TRAIL polynucleotide for use in gene therapy in treating cancer. One cannot extrapolate the teaching in the specification to the claims, because the state of the art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in

this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 28-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonavida, B et al, 1999, *Intl J Oncology*, 15(4): 793-802, or Yu et al, 2000, *Cancer Res*, 60: 2384-2389, IDS # 128, submitted on 11/12/02, or Gliniak B et al, 1999, *Cancer Res*, 59 (24): 6153-6158M, in view of Fathy El Etreby et al, 2000, *The Prostate* 42: 99-106,

IDS # 27, submitted on 11/12/02 or Koide SS et al, J Reproductive Medicine, 1998, 43(7): 551-560, IDS # 53, submitted on 11/12/02.

Claims 28-44 are drawn to :

A composition or a kit for treating cancer, comprising an effective amount of TRAIL and an antiprogestin sufficient to induce apoptosis in at least a portion of cancer cells exposed to said composition (Claims 28, 42). Said antiprogestin comprises Mifepristone (Claims 29, 30, 43). Said Mifepristone and said TRAIL are packaged such that Mifepristone is at least partially released for application to cancer prior to the release of said TRAIL, or are released substantially simultaneously (Claim 32). The dose of TRAIL results in a local concentration of TRAIL at the tumor, which ranges from 1 to 1,000 ng/ml, 200-600 ng/ml, 350-450 ng/ml (Claims 33-35). The dose of Mifepristone results in a local concentration of TRAIL at the tumor, which ranges from 1 to 1,000 uM, or 1 to 100 uM or 5 to 20 uM (Claims 36-38). Said cancer cells comprise prostate cancer cells, or androgen responsive cells, or prostate cells that do not respond to androgen (claims 39-41, 44).

Bonavida, B et al teach that human mammary adenocarcinoma cells in vivo and several tumor cells are sensitive to TRAIL-mediated apoptosis (p.795, second column under Biological activies of TRAIL, and p. 796). Bonavida, B et al teach that TRAIL apoptosis involves crossing of TRAIL receptors with the ligand TRAIL (p.794, second column, last paragraph). Bonavida, B et al teach that however tumor cells could develop resistance to TRAIL, and a combination therapy of TRAIL with chemotherapeutic drugs could reverse the resistance to TRAIL (p.797, first column).

Bonavida, B et al further teach that although TRAIL could be used to effectively treat sensitive prostate cell lines such as CEM, at 500 ng/ml, there is less than 5% of cytotoxicity in prostate cancer cells DU145, PC3 and LNCaP that become resistant to TRAIL, when treated at high concentration of TRAIL at 500 ng/ml (p. 798-799).

Bonavida, B et al do not teach a combination of TRAIL and an antiprogestin or Mifepristone. Bonavida, B et al do not teach that Mifepristone and TRAIL are packaged such that Mifepristone is at least partially released for application to cancer prior to the release of said TRAIL, or are released substantially simultaneously. Bonavida, B et al do not teach that the dose of TRAIL results in a local concentration of TRAIL at the tumor, which ranges from 1 to 1,000 ng/ml, 200-600 ng/ml, 350-450 ng/ml (Claims 33-35). Bonavida, B et al do not teach that the dose of Mifepristone results in a local concentration of TRAIL at the tumor, which ranges from 1 to 1,000 uM, or 1 to 100 uM or 5 to 20 uM

Yu et al teach that TRAIL induces cell death in androgen-independent prostate cancer cells PC-3 and DU145. Yu et al teach that induction of apoptosis by TRAIL is mediated by a cell death receptor, DR4, and the downstream caspases.

Gliniak et al teach that TRAIL can induce apoptosis in a wide variety of transformed human cells in vitro, and that colon carcinoma displays sensitivity to TRAIL in vivo that parallel their susceptibility to TRAIL-induced apoptosis in vitro.

Fathy El Etreby et al teach antitumor activity of Mifepristone in both androgen-sensitive (LNCaP) and androgen-insensitive (LNCaP-C4-2) human prostate cancer cells, grown in nude mice (see Results on pages 102-103). Fathy El Etreby et al teach

that there are high levels of progestrone receptors in prostate cancers and metastatic prostate cancers (p.100, first column, second paragraph), and that Mifepristone is an antiprogestin or progesterone receptor antagonist, which inhibits progestone-dependent processes (page 99, under Introduction). Fathy El Etreby et al teach that the antitumor action of antiprogestins is mediated via the progesterone receptor, and related to induction of apoptosis (p.100, first column, first paragraph).

Koide et al teach that Mifepristone could be used for treating leiomyoma, meningioma, and Cushing's Syndrome (p.553, second column, last paragraph, p.554-555).

It would have been *prima facia* obvious for one of ordinary skill in the art at the time the invention was made to combine TRAIL, taught by Bonavida, B et al or Yu et al, or Gliniak et al with Mifestrone taught by Fathy El Etreby et al, or Koide et al for use in treating cancer, including prostate cancer, which are either androgen responsive or non-responsive because of the following reasons:

- 1) Combination therapy of different types of therapeutic agents is common in the art, and in this particular case, since TRAIL and Mifestrone induce apoptosis of cancer cells, such as prostate cancer cells, by different mechanisms, they would be complementary to each other, and would increase the chance of killing cancer cells, and
- 2) Some cancer cells including prostate cancer cells could become resistant to TRAIL, and would benefit from the combination therapy of TRAIL and Mifestrone, because they would likely be killed by the complementary Mifestrone, which acts by a

different route than TRAIL, and could kill cancer cells, including androgen sensitive or insensitive prostate cancer cells.

It would have been obvious to package TRAIL and Mifepristone, such that Mifepristone is partially released prior to the release of TRAIL or both are released simultaneously, because such mode of operation is common in the art when a combination of drugs are used, to increase the effectiveness of the drugs.

With regards to the amounts of TRAIL or Mifepristone recited in claims 33-38, to determine optimum concentration of reactants is within the level of ordinary skill in the art. See In re Kronig, 190 USPQ 425.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS
October 05, 2004

SUSAN UNGAR, PH.D
PRIMARY EXAMINER
Susan U